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(54) Title: NOVEL MATRIX METALLOPROTEASE INHIBITORS

(57) Abstract: The present invention provides novel compounds of Formula I, pharmaceutically acceptable salts and N-oxides thereof, which are useful as Matric Metalloprotease (MMP) inhibitors. Also included in the present invention is the method fo using compounds of Formula I and therapeutic use of the compounds of Formula I.

NOVEL MATRIX METALLOPROTEASE INHIBITORS

FIELD OF INVENTION

The present invention relates to compounds of Formula I which are useful as Matrix Metalloprotease (MMP) inhibitors.

BACKGROUND OF THE INVENTION

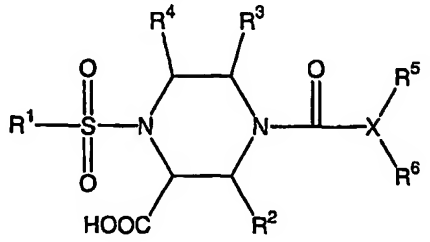
Matrix metalloproteases (MMPs) and their inhibitors (MMPIs) remain an area of interest for research in the Pharmaceutical Industry. Excess MMP activity is believed to contribute to a variety of diseases that involve extra-cellular matrix degradation such as rheumatoid arthritis, cancer metastasis, angiogenesis, pulmonary emphysema and periodontal disease. These diseases elude treatment and a cure has been elusive.

There is thus a need for MMPIs that can help treat diseases like arthritis, cancer, and emphysema, mentioned above. One way of going about discovering useful MMPIs would be to find molecules that would target a distinct sub-class of MMPs, i.e., the membrane-type matrix metalloproteases (MT-MMP). These enzymes differ from other MMPs in that they contain a transmembrane domain that anchors the enzyme to the cell surface. The implication is that the invasive phenotype is due to the combination of MT-MMP catalytic activity expressed in conjunction with a membrane anchor. Thus, inhibition of the specific MT-MMP activity may have profound effects on the ability of endothelial cells to migrate and may prevent angiogenesis.

The compounds of the present invention are useful as MT-MMP inhibitors. The compounds of the present thus have utility in treating diseases such as cancer, arthiritis, emphysema and other diseases associated with excess MMP activity.

SUMMARY OF THE INVENTION

This invention relates to a compound of Formula I:



Formula I

its prodrug and pharmaceutically acceptable salts thereof, wherein:

R^1 represents an aryl group substituted with zero to three groups selected from Ph, OPh, CH_2Ph, $C_{2\text{-}10}$ alkyl, O-$C_{1\text{-}10}$ alkyl, halogen, CF_3, COOH, OCF_3, and NHR^8;

R^2, R^3 and R^4 independently represent COOH, H, CH_2-O-CH_3, CO-$C_{1\text{-}4}$ alkyl, $C_{1\text{-}6}$ alkyl, aryl, or halogen;

X represents N, CH, or CR^9;

R^5 represents an aryl, cycloalkyl or a heteroaryl group, wherein said aryl, cycloalkyl and heteroaryl groups are independently substituted with one to four substituents selected from H, halogen, $C_{1\text{-}4}$ alkyl, NO_2, CN, OH, COOH, O-$C_{1\text{-}4}$ alkyl, S-$C_{1\text{-}4}$ alkyl, NH_2, NH-$C_{1\text{-}4}$ alkyl, N($C_{1\text{-}4}$ alkyl)$_2$, $CONH_2$, COO-$C_{1\text{-}3}$ alkyl, and CONH($C_{1\text{-}4}$ alkyl);

R^6 represents H, $C_{1\text{-}4}$ alkyl, aryl, cycloalkyl or a heteroaryl group, wherein said aryl, cycloalkyl and heteroaryl groups are independently substituted with one to four substituents selected from H, halogen, $C_{1\text{-}4}$ alkyl, NO_2, CN, OH, COOH, O-$C_{1\text{-}4}$ alkyl, S-$C_{1\text{-}4}$ alkyl, NH_2, NH-$C_{1\text{-}4}$ alkyl, N($C_{1\text{-}4}$ alkyl)$_2$, $CONH_2$, COO-$C_{1\text{-}3}$ alkyl, and CONH($C_{1\text{-}4}$ alkyl);

R^8 is selected from H, $C_{1\text{-}4}$ alkyl, and $COC_{1\text{-}4}$ alkyl; and

R^9 is selected from $C_{1\text{-}3}$ alkyl, $COC_{1\text{-}3}$ alkyl.

The present invention also provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I in combination with a pharmaceutically acceptable excipient, and method for treating a disease in an animal in which inhibition of MMP activity contributes to the pathology and/or symptomatology of the disease.

DETAILED DESCRIPTION OF THE INVENTION

The present invention in one of its preferred embodiment provides a compound of Formula I wherein:

R^1 represents a phenyl or naphthyl group, said phenyl and naphthyl group substituted with zero to two groups selected from C_{1-4} alkyl, halogen, COOH, Ph and NH_2;

R^2, R^3 and R^4 independently represent COOH or H;

X represents CH, N, or $C(CH_3)$;

R^5 and R^6 independently represent a phenyl, cyclohexyl or naphthyl group substituted with one to three substituents selected from H, halogen, COOH, NH_2, N-C_{1-4} alkyl, and $CONH_2$.

A further preferred embodiment provides a compound of Formula I selected from:

4-Diphenylacetyl-1-(6-methoxy-naphthalene-2-sulfonyl)-piperazine-2-carboxylic acid;

4-Diphenylacetyl-1-(naphthalene-2-sulfonyl)-piperazine-2-carboxylic acid;

4-Diphenylacetyl-1-(4-fluoro-benzenesulfonyl)-piperazine-2-carboxylic acid;

4-Diphenylacetyl-1-(4-methoxy-benzenesulfonyl)-piperazine-2-carboxylic acid;

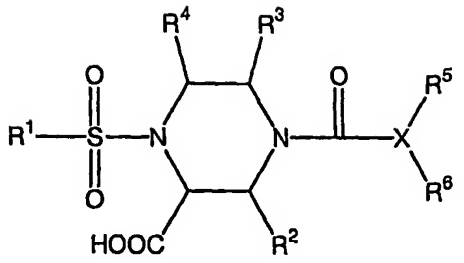
4-Diphenylacetyl-1-(toluene-4-sulfonyl)-piperazine-2-carboxylic acid;

1-(Naphthalene-2-sulfonyl)-4-(2-phenyl-propionyl)-piperazine-2-carboxylic acid;

1-(Naphthalene-2-sulfonyl)-4-(2-phenyl-propionyl)-piperazine-2-carboxylic acid; and

4-(2,2-Dicyclohexyl-acetyl)-1-(naphthalene-2-sulfonyl)-piperazine-2-carboxylic acid.

Another aspect of the present invention provides a method of treating a disease in an animal in which MMP activity contributes to the pathology and/or symptomatology of the disease, which method comprises administering to the animal a therapeutically effective amount of compound of Formula I:



Formula I

its prodrug and pharmaceutically acceptable salts thereof, wherein:

R^1 represents an aryl group substituted with zero to three groups selected from Ph, OPh, CH_2Ph, $C_{2\text{-}10}$ alkyl, O-$C_{1\text{-}10}$ alkyl, halogen, CF_3, COOH, OCF_3, and NHR^8;

R^2, R^3 and R^4 independently represent COOH, H, CH_2-O-CH_3, CO-$C_{1\text{-}4}$ alkyl, $C_{1\text{-}6}$ alkyl, aryl, or halogen;

X represents N, CH, or CR^9;

R^5 represents an aryl, cycloalkyl or a heteroaryl group, wherein said aryl, cycloalkyl and heteroaryl groups are independently substituted with one to four substituents selected from H, halogen, $C_{1\text{-}4}$ alkyl, NO_2, CN, OH, COOH, O-$C_{1\text{-}4}$ alkyl, S-$C_{1\text{-}4}$ alkyl, NH_2, NH-$C_{1\text{-}4}$ alkyl, N($C_{1\text{-}4}$ alkyl)$_2$, $CONH_2$, COO-$C_{1\text{-}3}$ alkyl, and CONH($C_{1\text{-}4}$ alkyl);

R^6 represents H, $C_{1\text{-}4}$ alkyl, aryl, cycloalkyl or a heteroaryl group, wherein said aryl, cycloalkyl and heteroaryl groups are independently substituted with one to four substituents selected from H, halogen, $C_{1\text{-}4}$ alkyl, NO_2, CN, OH, COOH, O-$C_{1\text{-}4}$ alkyl, S-$C_{1\text{-}4}$ alkyl, NH_2, NH-$C_{1\text{-}4}$ alkyl, N($C_{1\text{-}4}$ alkyl)$_2$, $CONH_2$, COO-$C_{1\text{-}3}$ alkyl, and CONH($C_{1\text{-}4}$ alkyl);

R^8 is selected from H, $C_{1\text{-}4}$ alkyl, and $COC_{1\text{-}4}$ alkyl; and

R^9 is selected from $C_{1\text{-}3}$ alkyl, $COC_{1\text{-}3}$ alkyl.

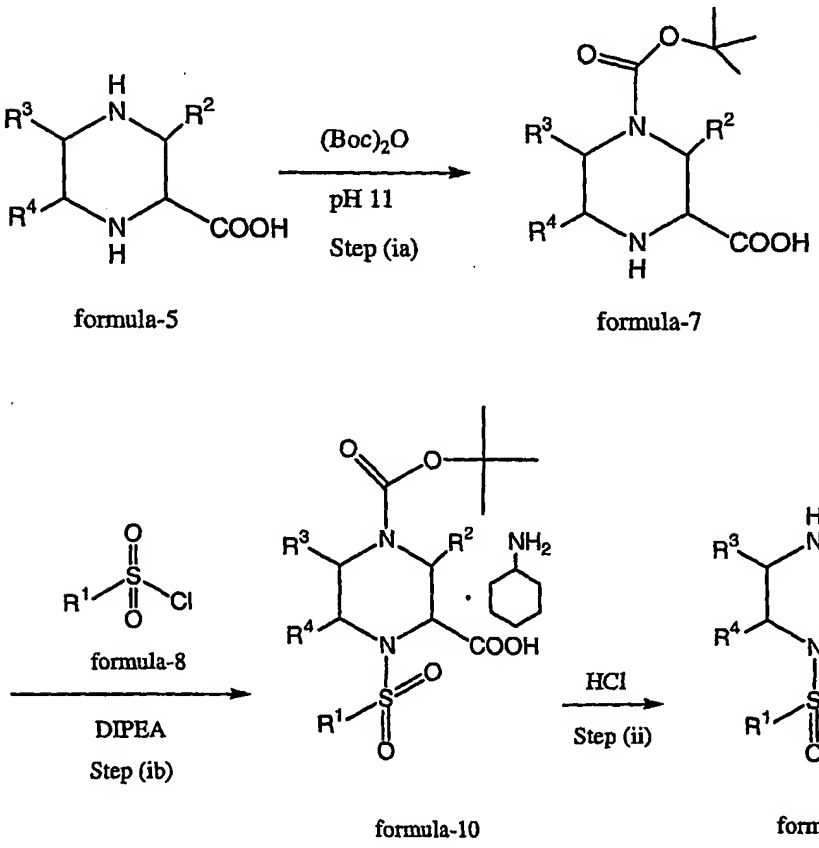
Yet another aspect of the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 in combination with a pharmaceutically acceptable excipient. Also provided in one of the aspect of the present invention is a method for treating a disease in an animal in which inhibition of MMP can prevent, inhibit or ameliorate the pathology and/or symptomatology of the disease, which method comprises administering to the animal a therapeutically effective amount of compound of Claim 1 or a *N*-oxide derivative or

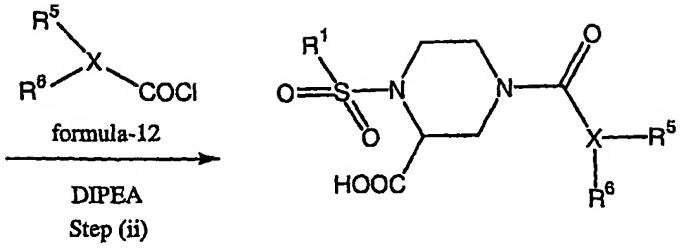
individual isomer or mixture of isomers thereof; or a pharmaceutically acceptable salt thereof.

Experimental

Compounds of the present invention can be synthesized by procedures known to one skilled in the art. The following illustrative synthetic scheme outlines a method that can be used to synthesize compounds of the present invention.

Scheme I





Formula I

Step (ia)

A mixture of a compound of formula-5 (e.g., piperazine-2-carboxylic acid) (1 eq.) and 30%NaOH is maintained at a pH of about 11. Solid $(BOC)_2O$ (1 eq.) then is added to the above mixture, with stirring, while maintaining the pH at about 11, by adding 30%NaOH solution as necessary. The resulting reaction then is acidified using Amberlite 120 acidic ion exchange resin until the pH of the reaction mixture is 4.5. The reaction mixture then is filtered and the aqueous filtrate is washed with ether (x4). The washed aqueous layer then is concentrated under reduced pressure to yield a compound of formula-7 (e.g., 4-BOC-piperazine-2-carboxylic acid).

Step (ib)

A mixture (suspension) of a compound of formula-7 (1 eq.) and methylene chloride is mixed with DIPEA (3 eq.) to form a clear reaction mixture. The clear reaction mixture is maintained at a temperature of about 0°C as a compound of formula-8 (e.g., 2-naphthalenesulfonyl chloride) (about 1.1 eq.) is added in portions while maintaining the temperature of the reaction mixture at about 0°C. Addition of the compound of formula-8 is accomplished over a period of about 30 minutes. The resulting reaction mixture then is agitated for about 2 hours resulting in the dissolution of all the reaction solids. The reaction mixture then is washed with a 10% aqueous solution of $NaHSO_4$ (x4), dried ($MgSO_4$) and concentrated under reduced pressure to yield a residue. The residue is diluted with ether and cyclohexyl amine (about 3-3.5 eq.). The resulting reaction mixture is agitated for about 30 minutes leading to the formation of a solid. The solid is isolated, washed with ether and dried to afford the product of formula-10.

Step (ii)

A mixture of a compound of formula-10 (0.62 mmol) and ethyl acetate is washed with several portions of 0.5M HCl and brine, and then dried (Na_2SO_4). The reaction mixture then is concentrated under reduced pressure to yield a foamy material. This foamy material is diluted with methylene chloride, cooled (0° C) under nitrogen, and then treated with an excess of 4 M HCl in dioxane. The mixture is allowed to stir for 2 hours. Conversion of the compound of formula-10 to a compound of formula-11 is determined by TLC analysis. An additional amount of hydrochloric acid is added to the reaction mixture and the reaction mixture is agitated for an additional one hour at ambient temperature or refluxed for about 15 minutes, if the conversion of the compound of formula-10 to formula-11 is not complete.

The reaction mixture then is diluted with ethyl ether leading to the formation of a precipitate. The precipitate is isolated, rinsed with ethyl ether and under reduced pressure to yield a compound of formula-11.

Step (iii)

A mixture of a compound of formula-11 (1 eq.) and THF is agitated at about 0°C and under a nitrogen atmosphere. To the cooled reaction mixture then is added DIPEA (1.1 eq.), in portions, over a period of about ten minutes. The resulting reaction mixture is agitated at about 0°C for an additional ten minutes. The agitated reaction mixture then is combined with a compound of formula-12 (1 eq.) and the reaction mixture is gradually warmed to ambient temperature and then agitated for about 2 hours. The progress of the conversion of a compound of formula-11 to Formula I is checked by TLC. The preceding procedure is repeated until the conversion of the compound of formula-11 to a compound of Formula I is quantitative.

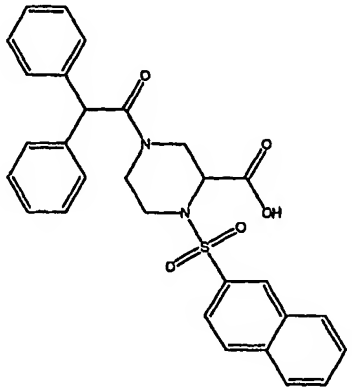
The reaction mixture then is diluted with ethyl ether and then sequentially washed with 1M HCl, water, and brine. The ether layer then is dried (Na_2SO_4), filtered and concentrated under reduced pressure to yield a foamy residue. The residue is purified by chromatographic techniques known to one skilled in the art, e.g., column chromatography, to yield a compound of Formula I.

The following examples were made using the synthetic Scheme I, discussed above:

Examples

Example 1

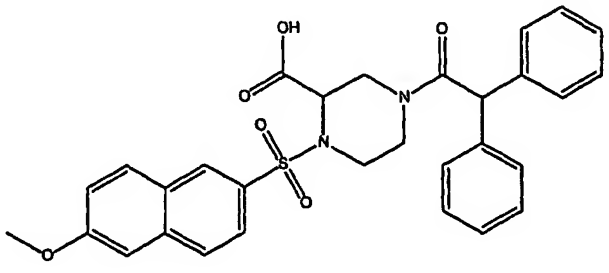
4-Diphenylacetyl-1-(naphthalene-2-sulfonyl)-piperazine-2-carboxylic acid



NMR (^{1}H-300MHz, DMSO-d_6) δ(ppm): (represents a mixture of cis/trans conformers) 8.42 (m, 1H), 8.15-7.97 (m, 3H), 7.81-7.60 (m, 3H), 7.33-6.96 (m, 10H), 5.38 (ss, 1H), 4.91-4.52 (m, 1H), 4.36-3.79 (m, 1H), 3.71-3.43 (m, 1H), 3.25-2.51 (m, 4H). MS (ES) calc. 514.6, found 515.2 (M+H).

Example 2

4-Diphenylacetyl-1-(6-methoxy-naphthalene-2-sulfonyl)-piperazine-2-carboxylic acid

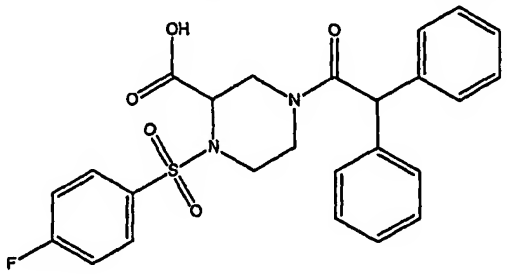


NMR (^{1}H-300MHz, DMSO-d_6): δ: 8.34 (s, 1H), 7.95-7.70 (m, 3H), 7.35-7.00 (m, 12H), 5.64 (s, 1H), 5.33 (s, 1H), 4.93-4.20 (m, 3H), 3.84 (s, 3H), 3.55-3.22 (m, 2H), 2.66 (m, 1H), 2.31 (m, 1H). EM = 544.17;

MS (ESI sciex): +m/z = 545.0; -m/z = 543.0.

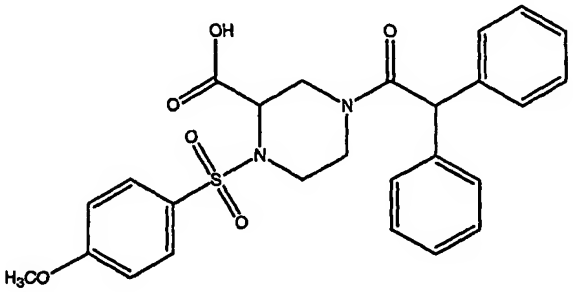
Example 3

4-Diphenylacetyl-1-(4-fluoro-benzenesulfonyl)-piperazine-2-carboxylic acid



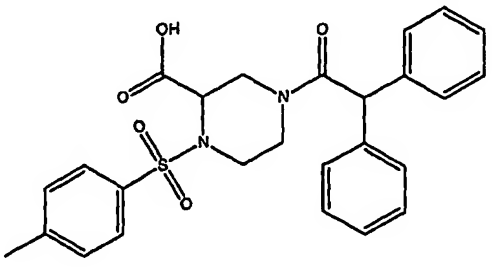
Example 4

4-Diphenylacetyl-1-(4-methoxy-benzenesulfonyl)-piperazine-2-carboxylic acid



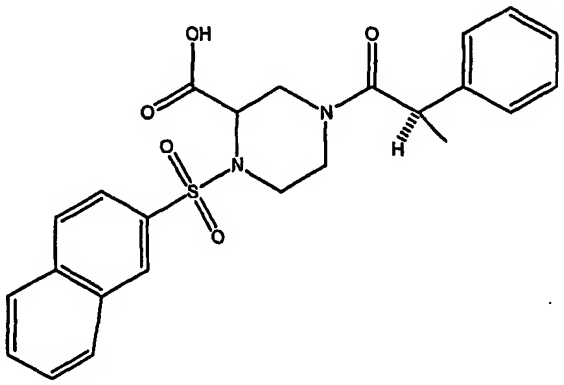
Example 5

4-Diphenylacetyl-1-(toluene-4-sulfonyl)-piperazine-2-carboxylic acid



Example 6

1-(Naphthalene-2-sulfonyl)-4-(2-phenyl-propionyl)-piperazine-2-carboxylic acid

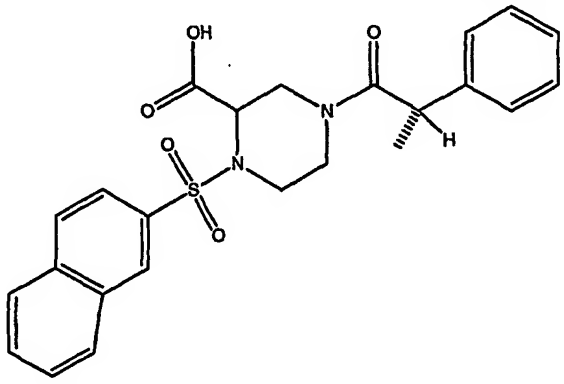


NMR (^{1}H-300MHz, DMSO-d_6) δ: 8.48 (m, 1H), 8.13-7.97 (m, 3H), 7.88-7.60 (m, 3H), 7.31-7.05 (m, 5H), 4.88 (m, 1H), 4.57-3.20 (m, 4H), 2.65-2.20 (m, 4H), 1.14 (d, 3H, J = 6.8 Hz). EM = 452.14;

MS (ESI sciex): +m/z = 453.0; -m/z = 450.6.

Example 7

1-(Naphthalene-2-sulfonyl)-4-(2-phenyl-propionyl)-piperazine-2-carboxylic acid

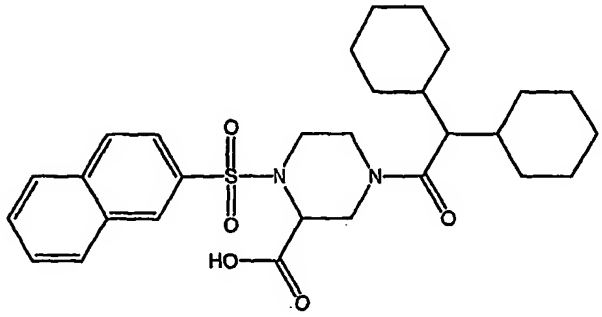


NMR (^{1}H-300MHz, DMSO-d_6) δ: 8.48 (m, 1H), 8.13-7.97 (m, 3H), 7.88-7.60 (m, 3H), 7.31-7.05 (m, 5H), 4.88 (m, 1H), 4.57-3.20 (m, 4H), 2.65-2.20 (m, 4H), 1.14 (d, 3H, J = 6.8 Hz). EM = 452.14;

MS (ESI sciex): +m/z = 453.0; -m/z = 450.6.

Example 8

4-(2,2-Dicyclohexyl-acetyl)-1-(naphthalene-2-sulfonyl)-piperazine-2-carboxylic acid



NMR (^{1}H-300MHz, DMSO-d_6) δ: 8.48 (s, 1H), 8.19-8.00 (m, 2H), 7.84 (m, 1H), 7.72-7.61 (m, 2H), 4.85 (m, 1H), 4.49-4.05 (m, 4H), 3.85-2.74 (m, 4H), 1.66-0.70 (m, 22H). EM = 526.25;

MS (ESI sciex): +m/z = 527.2; -m/z = 525.0.

UTILITY

Assay:

Kinetic measurements are performed in 96-well U-bottom microtiter plates (Falcon) using a kinetic plate reader (Fmax, Molecular Devices). MT1-MMP (1.6 nM) or MMP-2 (4 nM) is combined with inhibitor at varying concentrations in 50 mM Tris (pH 7.4), 150 mM NaCl, 5 mM $CaCl_2$, 10 μM $ZnCl_2$, 0.05 % Tween-20 and 10% DMSO for 30 minutes at room temperature. Reactions are initiated by the addition of substrate (20μM, 7-methoxycoumarin-4-acetyl-Pro-Lue-Gly-Leu-beta-(2,4-dinitrophenyl-amino)Ala-Ala-Arg-amide) and the rate of substrate hydrolysis is measured by monitoring the change in fluorescence (ex 355, em 460) over five minutes. Ki apparent (Ki') calculations are performed by a non-linear regression fit to the Morrison equation as described (1).

Assay Reagents:

MT1-MMP and MMP-2 were purchased from a commercial vendors (Chemicon International and CalBiochem).

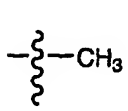
MMP substrate, 7-methoxycoumarin-4-acetyl-Pro-Lue-Gly-Leu-beta-(2,4-dinitrophenyl-amino)Ala-Ala-Arg-amide, and assay buffer reagents were purchased from Sigma.

DEFINITIONS

"Alkyl" and "Alkylene": The terms "alkyl" and "alkylene" as used herein represent a saturated or partially unsaturated straight chain or branched hydrocarbon group having from one (1) to fourteen (14) carbon atoms, unless indicated otherwise. Illustrative examples of an alkyl group are methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, *tert*-butyl, vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methylallyl, ethynyl, 1-propynyl, 2-propynyl, and the like. Illustrative examples of an alkylene group are methylene, ethylene, propylene, isopropylene, butylene, propenylene, butenylene, ethynelene, propynylene, butynylene and the like. An alkyl or alkylene group is substituted with one to four groups selected from hydrogen, halogen, nitro, cyano, $-OR^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-C(O)NR^{11}R^{11}$, $-S(O)_2NR^{11}R^{11}$, $-X^7NR^{11}R^{11}$, $-X^7NR^{11}C(O)OR^{11}$, $-X^7NR^{11}C(O)NR^{11}R^{11}$ or $-X^7NR^{11}C(NR^{11}NR^{11}R^{11}$, wherein X^7 represents is a bond or $-(CH_2)_{1-6}-$ and each R^{11} independently is hydrogen or $-(C_{1-6})$alkyl.

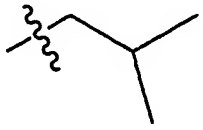
The following representations further illustrate the terms "alkyl" and "alkylene".

"Alkyl":

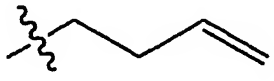


methyl

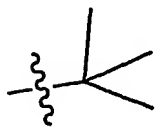
ethyl



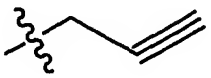
iso-butyl



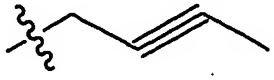
1-butenyl



t-butyl

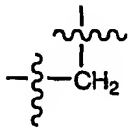


1-propynyl

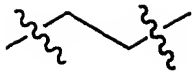


2-butynyl

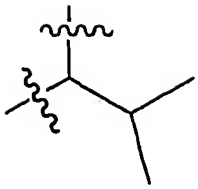
"Alkylene"



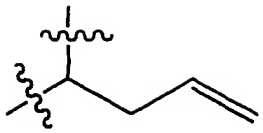
methylene



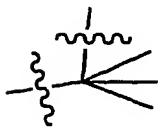
ethylene



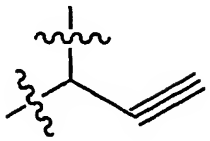
iso-butylene



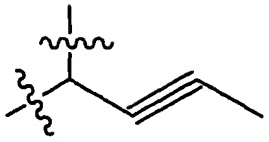
1-butenyl



t-butylene



1-propynylene

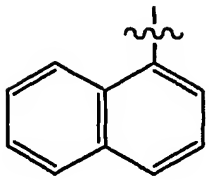


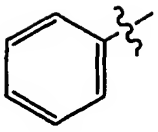
2-butynylene

"Aryl": The terms "aryl" or "arylene" as used herein represent a monocyclic, bicyclic, or tricyclic aromatic moiety having from five (5) to fourteen (14) carbon atoms, unless indicated otherwise. The aromatic moiety can be fused a ring (e.g., naphthalene) or a bicyclic ring system wherein two aromatic rings are connected to each other by a bond (e.g., biphenyl). Illustrative examples of a monocyclic aromatic moiety are phenyl and cyclopentadienyl, of a fused bicyclic aromatic moiety is naphthyl and of a fused tricyclic aromatic moiety is anthracyl. An aryl or arylene moiety is substituted with one to four groups selected from hydrogen, halogen, nitro, cyano, C_{1-8} straight chain alkyl, C_{3-14} branched alkyl, $-OR^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-C(O)NR^{11}R^{11}$, $-S(O)_2NR^{11}R^{11}$, $-X^7NR^{11}R^{11}$, $-X^7NR^{11}C(O)OR^{11}$, $-X^7NR^{11}C(O)NR^{11}R^{11}$ or $-X^7NR^{11}C(NR^{11}NR^{11}R^{11}$, wherein X^7 represents is a bond or $-(CH_2)_{1-6}-$ and each R^{11} independently is hydrogen or $-(C_{1-6})$alkyl.

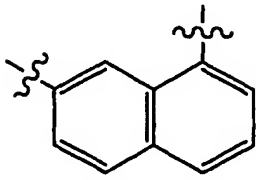
The following representations further illustrate the terms "aryl" and "arylene".

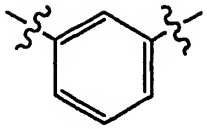
Aryl:





Arylene:



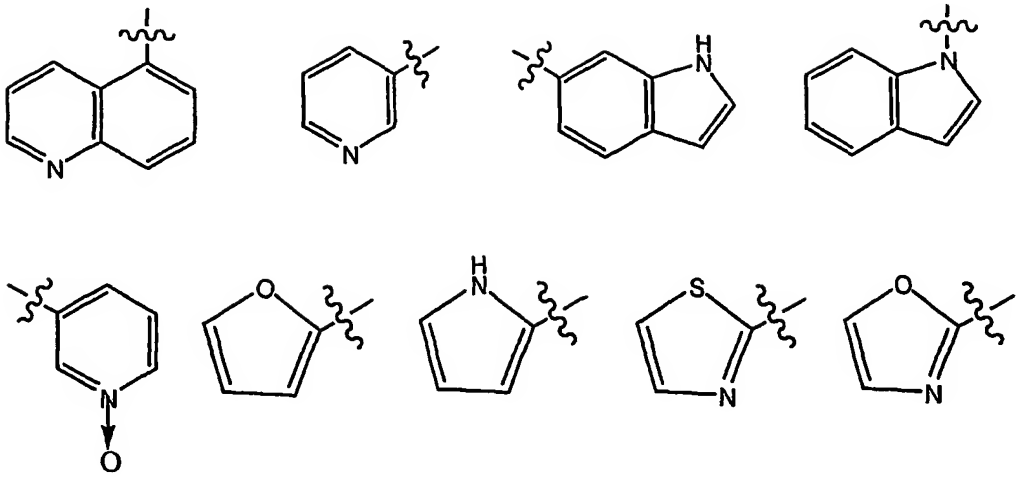


The term halogen represents one of Cl, Br, I and F. The term "Ph" represents a phenyl group.

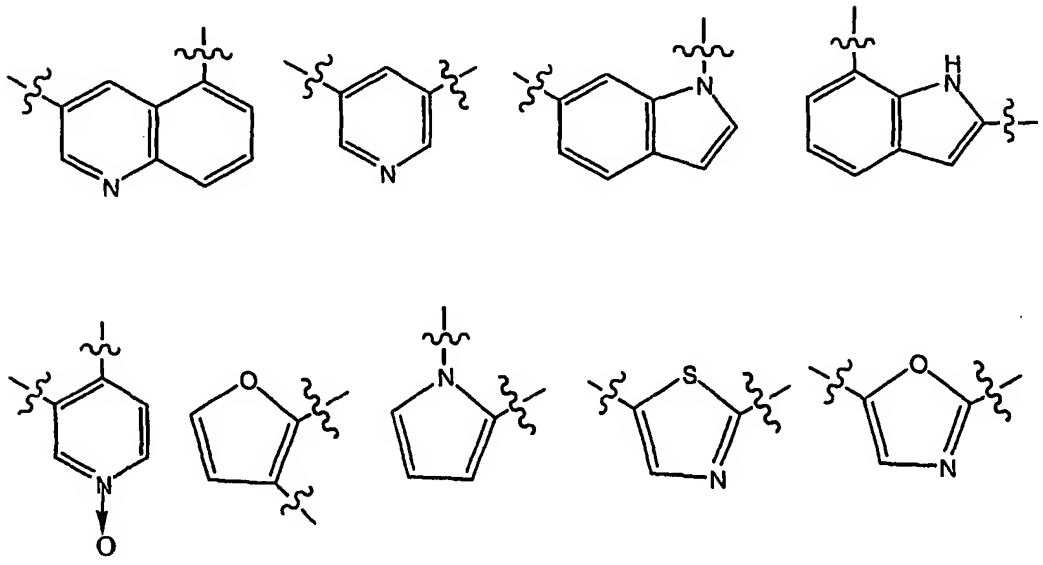
"Heteroaryl" : The terms "heteroaryl" and "heteroarylene" represent an "aryl" group as defined above but wherein at least one and maximum of six (6) carbon atoms in an aryl group are replaced with a hetero atom selected from S, O and N. The hetero atoms can exist in their respective oxidized states. Thus a Sulfur (S) atom can exist as a sulfoxide or sulfone, while a Nitrogen (N) can exist as in the form of an N-oxide group. Illustrative examples of a "heteroaryl" group are thienyl, furyl, pyrrolyl, pyrimidinyl, isoxazolyl, oxaxolyl, indolyl, benzo[*b*]thienyl, isobenzofuranyl, purinyl, isoquinolyl, pterdinyl, perimidinyl, imidazolyl, 1-methylimidazolyl, 1-benzylimidazolyl, pyridyl, pyrazolyl, pyrazinyl, quinolyl, [2,4']bipyridinylyl, 2-phenylpyridyl, 4-thiazol-4-ylphenyl, and the like. As in the case of an "aryl" group above, a "heteroaryl" group or moiety is substituted with one to four groups selected from hydrogen, halogen, nitro, cyano, C_{1-8} straight chain alkyl, C_{3-14} branched alkyl, $-OR^{11}$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-C(O)NR^{11}R^{11}$, $-S(O)_2NR^{11}R^{11}$, $-X^7NR^{11}R^{11}$, $-X^7NR^{11}C(O)OR^{11}$, $-X^7NR^{11}C(O)NR^{11}R^{11}$ or $-X^7NR^{11}C(NR^{11}NR^{11}R^{11}$, wherein X^7 represents is a bond or $-(CH_2)_{1-6}-$ and each R^{11} independently is hydrogen or $-(C_{1-6})$alkyl.

The following representations further illustrate the terms "heteroaryl" and "heteroarylene".

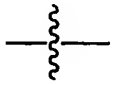
Heteroaryl:



Heteroarylene:



As used in the present invention, the illustration:



generally indicates a point of attachment of the group, comprising the illustration, to another group or atom.

The *N*-oxides of compounds of Formula I can be prepared by methods known to those of ordinary skill in the art. For example, *N*-oxides can be prepared by treating an unoxidized form of the compound of Formula I with an oxidizing agent (e.g., trifluoroperacetic acid, permaleic acid, perbenzoic acid, peracetic acid, *meta*-chloroperoxybenzoic acid, or the like) in a suitable inert organic solvent (e.g., tetrahydrofuran (THF), ethyl acetate, methylene chloride, and the like) at a suitable temperature ranging from about -20°C to about 30°C. Alternatively, the *N*-oxides of the compounds of Formula I can be prepared from the *N*-oxide of an appropriate starting material.

Compounds of Formula I in their unoxidized form can be prepared from *N*-oxides of compounds of Formula I by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in a suitable inert organic solvent (e.g., acetonitrile, ethanol, aqueous dioxane, or the like) at a temperature ranging from about 0°C to about 80°C.

"Pharmaceutically Acceptable Salts": The term "pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" means salts of compounds of Formula I which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, *o*-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, madelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, *p*-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid),

3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid and the like.

Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, trimethamine, *N*-methylglucamine and the like.

"Prodrug derivatives" means derivatives of compounds of Formula I which are converted *in vivo* to the corresponding non-derivatized form of a compound of Formula I.

"Therapeutically Effective Amount": The term "therapeutically effective amount" means that amount which, when administered to an animal for treating a disease, is sufficient to effect such treatment for the disease.

"Treatment" or Treating": The terms "treatment" or "treating" means any administration of a compound of the present invention and includes:

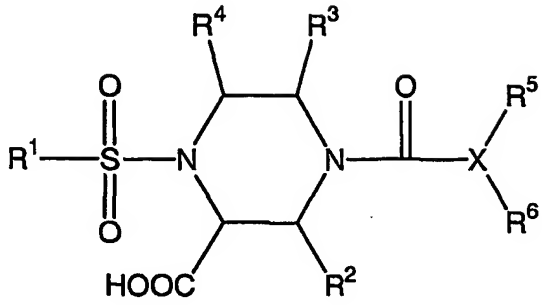
(1) preventing the disease from occurring in an animal which may be predisposed to the disease but does not yet experience or display the pathology or symptomatology of the disease,

(2) inhibiting the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., arresting further development of the pathology and/or symptomatology), or

(3) ameliorating the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., reversing the pathology and/or symptomatology).

CLAIMS

1. A compound of Formula I



Formula I

its prodrug and pharmaceutically acceptable salts thereof, wherein:

R^1 represents an aryl group substituted with zero to three groups selected from Ph, OPh, CH_2Ph, C_{2-10} alkyl, O-C_{1-10} alkyl, halogen, CF_3, COOH, OCF_3, and NHR^8;

R^2, R^3 and R^4 independently represent COOH, H, CH_2-O-CH_3, CO-C_{1-4} alkyl, C_{1-6} alkyl, aryl, or halogen;

X represents N, CH, or CR^9;

R^5 represents an aryl, cycloalkyl or a heteroaryl group, wherein said aryl, cycloalkyl and heteroaryl groups are independently substituted with one to four substituents selected from H, halogen, C_{1-4} alkyl, NO_2, CN, OH, COOH, O-C_{1-4} alkyl, S-C_{1-4} alkyl, NH_2, NH-C_{1-4} alkyl, N(C_{1-4} alkyl)$_2$, $CONH_2$, COO-C_{1-3} alkyl, and CONH(C_{1-4} alkyl);

R^6 represents H, C_{1-4} alkyl, aryl, cycloalkyl or a heteroaryl group, wherein said aryl, cycloalkyl and heteroaryl groups are independently substituted with one to four substituents selected from H, halogen, C_{1-4} alkyl, NO_2, CN, OH, COOH, O-C_{1-4} alkyl, S-C_{1-4} alkyl, NH_2, NH-C_{1-4} alkyl, N(C_{1-4} alkyl)$_2$, $CONH_2$, COO-C_{1-3} alkyl, and CONH(C_{1-4} alkyl);

R^8 is selected from H, C_{1-4} alkyl, and COC_{1-4} alkyl; and

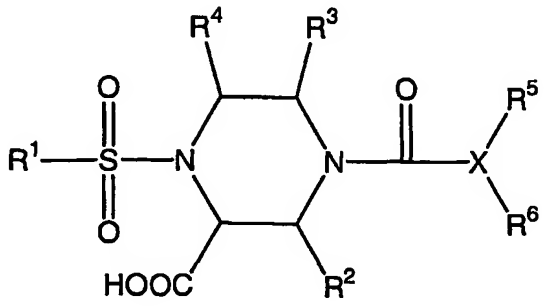
R^9 is selected from C_{1-3} alkyl, COC_{1-3} alkyl.

2. A compound of Claim 1 wherein:

R^1 represents a phenyl or naphthyl group, said phenyl and naphthyl group substituted with zero to two groups selected from C_{1-4} alkyl, halogen, COOH, Ph and NH_2;
R^2, R^3 and R^4 independently represent COOH or H;
X represents CH, N, or $C(CH_3)$;
R^5 and R^6 independently represent a phenyl, cyclohexyl or naphthyl group substituted with one to three substituents selected from H, halogen, COOH, NH_2, N-C_{1-4} alkyl, and $CONH_2$.

3. A compound of Claim 1 selected from:
4-Diphenylacetyl-1-(6-methoxy-naphthalene-2-sulfonyl)-piperazine-2-carboxylic acid;
4-Diphenylacetyl-1-(naphthalene-2-sulfonyl)-piperazine-2-carboxylic acid;
4-Diphenylacetyl-1-(4-fluoro-benzenesulfonyl)-piperazine-2-carboxylic acid;
4-Diphenylacetyl-1-(4-methoxy-benzenesulfonyl)-piperazine-2-carboxylic acid;
4-Diphenylacetyl-1-(toluene-4-sulfonyl)-piperazine-2-carboxylic acid;
1-(Naphthalene-2-sulfonyl)-4-(2-phenyl-propionyl)-piperazine-2-carboxylic acid;
1-(Naphthalene-2-sulfonyl)-4-(2-phenyl-propionyl)-piperazine-2-carboxylic acid; and
4-(2,2-Dicyclohexyl-acetyl)-1-(naphthalene-2-sulfonyl)-piperazine-2-carboxylic acid.

4. A method of treating a disease in an animal in which MMP activity contributes to the pathology and/or symptomatology of the disease, which method comprises administering to the animal a therapeutically effective amount of compound of Formula I:



Formula I

its prodrug and pharmaceutically acceptable salts thereof, wherein:

R^1 represents an aryl group substituted with zero to three groups selected from Ph, OPh, CH_2Ph, C_{2-10} alkyl, O-C_{1-10} alkyl, halogen, CF_3, COOH, OCF_3, and NHR^8;

R^2, R^3 and R^4 independently represent COOH, H, CH_2-O-CH_3, CO-C_{1-4} alkyl, C_{1-6} alkyl, aryl, or halogen;

X represents N, CH, or CR^9;

R^5 represents an aryl, cycloalkyl or a heteroaryl group, wherein said aryl, cycloalkyl and heteroaryl groups are independently substituted with one to four substituents selected from H, halogen, C_{1-4} alkyl, NO_2, CN, OH, COOH, O-C_{1-4} alkyl, S-C_{1-4} alkyl, NH_2, NH-C_{1-4} alkyl, N(C_{1-4} alkyl)$_2$, $CONH_2$, COO-C_{1-3} alkyl, and CONH(C_{1-4} alkyl);

R^6 represents H, C_{1-4} alkyl, aryl, cycloalkyl or a heteroaryl group, wherein said aryl, cycloalkyl and heteroaryl groups are independently substituted with one to four substituents selected from H, halogen, C_{1-4} alkyl, NO_2, CN, OH, COOH, O-C_{1-4} alkyl, S-C_{1-4} alkyl, NH_2, NH-C_{1-4} alkyl, N(C_{1-4} alkyl)$_2$, $CONH_2$, COO-C_{1-3} alkyl, and CONH(C_{1-4} alkyl);

R^8 is selected from H, C_{1-4} alkyl, and COC_{1-4} alkyl; and

R^9 is selected from C_{1-3} alkyl, COC_{1-3} alkyl.

5. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 in combination with a pharmaceutically acceptable excipient.

6. A method for treating a disease in an animal in which inhibition of MMP can prevent, inhibit or ameliorate the pathology and/or symptomatology of the disease, which method comprises administering to the animal a therapeutically effective amount of compound of Claim 1 or a *N*-oxide derivative or individual isomer or mixture of isomers thereof; or a pharmaceutically acceptable salt thereof.